Bandolier 155

Independent evidence-based thinking about health care

On quotations

Bandolier loves quotations. However complex a problem, or difficult a topic, an appropriate quotation can encapsulate it all in just a few choice words. A really good quotation does something more, though; it puts a spin on a thought, that can make you think almost, but not completely, differently about the topic in hand.

Sixteen years ago a paper was published that possibly had the greatest collection of quotable quotes than any other Bandolier has come across [1]. By Professor Geoffrey Rose on environmental health, it is even today worth a read, because it was packed with ideas about risk, and how we deal with it, as well as having a superabundance of quotes. Here are some of them:

- *All policy decision should be based on absolute measures of risk: relative risk is strictly for researchers only.*
- *The nature of the risk…tends to be more influential than its size, which is not very logical.*
- *You can' exclude the possibility you haven't considered.*
- *Many exposed to a small risk generate more cases than a few exposed to a high risk.*
- *The dogmatic certainty of experts is unforgivable.*
- *'Have not noticed' must never be mistaken for 'Is not there'.*

New year presents

Don't forget Bandolier's Little Book of Making Sense of the Medical Evidence available from Oxford University Press 0-19-856604-2 / 978-0-19-856604-5 £24.95

The present Bandolier wants from its readers is for them to keep the suggestions coming for topics to look at in 2007.

Reference:

1 G Rose. Environmental health: problems and prospects. Journal of the Royal College of Physicians of London 1991 25: 48-52.

In this issue

MINDSTRETCHER: NAC AND CIN IN CORONARY ANGIOGRAPHY

Contrast-induced nephropathy (CIN) is a complication of coronary angiography, usually defined biochemically by increased serum creatinine in the 48 hours after angiography. The incidence of CIN tends to be higher in patients with more severe renal dysfunction and diabetes. CIN is associated with increased morbidity, longer hospital stay, dialysis, and even mortality. There are several proposed mechanisms, including oxidative stress and reduced renal perfusion. N-acetylcysteine (NAC) has been considered to reduce the incidence of CIN, with evidence mainly from a meta-analysis of small trials [1]. A newer meta-analysis [2] does not find a statistically reduced incidence.

There are problems with clinical heterogeneity, including definition of renal impairment, and the proportion of patients with diabetes. Others are dose of contrast medium, and the dose and dosing regimen of NAC, which has typically been a pre-loading for one or two days before the procedure. As problems are always good learning opportunities, Bandolier decided to examine the evidence from the meta-analysis [2].

Systematic review

The review sought randomised trials published to November 2003 in three electronic databases, as well as abstracts from a number of international meetings published over the previous five years. Included studies had to be randomised, compare NAC (any regimen) against placebo, in patients undergoing coronary angiography and receiving intravenous fluids and low osmolarity non-ionic contrast media. CIN was defined as an increase in serum creatinine of at least 0.5 mg/dL (44 μmol/L) or an increase of at least 25% from baseline over 48 hours.

Results

Trials

The review [2] found 13 trials with 1,874 patients. Six of these were published only as abstracts (five of which have subsequently been published in full). They varied in size, creatinine concentrations for inclusion, the volume of contrast medium, and particularly the dosing regimen of NAC. Eleven used only oral NAC, while two used intravenous NAC. Almost all used NAC both before and after the procedure.

A brief PubMed search (December 2006) identified an additional eight randomised trials with 1,343 patients. These additional trials used different NAC regimens, with three using intravenous NAC, with or without oral NAC.

NAC effectiveness

Results for all 21 trials are shown in Figure 1, which demonstrates a wide variation in trial size (38 to 477 patients), CIN incidence with placebo (0% to 45%), and NAC effectiveness. Only five of the 21 trials individually showed a significant reduction in CIN incidence with NAC.

Various sensitivity analyses are shown in Table 1. There was a statistically significant reduction in CIN incidence for all 21 trials combined, for the 13 in the meta-analysis, for the eight subsequent trials, and for those using only oral NAC or intravenous NAC (sometimes with oral NAC also).

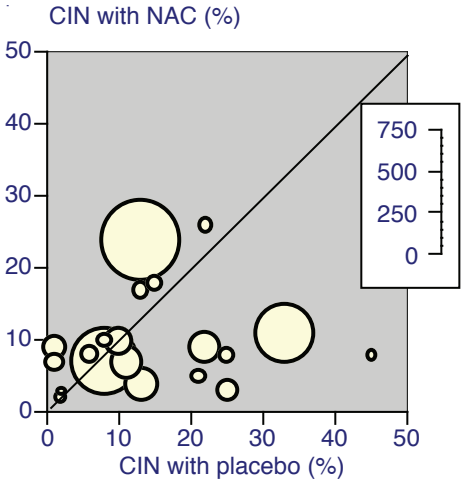
A sensitivity analysis was performed according to the CIN incidence with placebo. When the CIN incidence with placebo was below 25%, there was no significant reduction with NAC. When the CIN incidence with placebo was above 25% in four trials, there was a large reduction with NAC by about two thirds, producing a number needed to treat to prevent one case of CIN of 4.7 (95% CI 3.6 to 6.8).

Comment

There are many different lessons to be learned here:

1 Don't think that a systematic review and meta-analysis will be up to date even if it is just published. There is often a substantial gap between date of last search and print – in this case over two years. It is worthwhile doing some supplementary searching, especially in a hot topic area, as this is. Bandolier found eight more trials that increased the number of patients by 70% with a quick 10-minute search on PubMed. This time the additional information didn't change anything, but it could have.
2 Where there is clinical heterogeneity, and a result that is not exactly cast iron, consider what sensitivity analyses may be appropriate. Bandolier looked at oral and IV NAC, but others may be more appropriate.

Figure 1: Individual results from all 21 trials of NAC for CIN



3 Look at the data. Really, look at the data, not that in the paper but the raw data. This is where the L'Abbé plot (Figure 1) beats the forest plot in the meta-analysis [1] hands down. Just a glance at Figure 1 tells you that there is a consistent effect at higher control event rate – which is why Bandolier performed that sensitivity analysis.
4 If you have trials in which no event (or very few events) occur when you do nothing (with placebo), then it is going to be difficult to show any effect when you do something (in this case give NAC). Trials without events lack internal sensitivity.
5 The lesson is that we need to think not whether NAC works, but whether we can define what patients NAC works in. Bandolier is unable to provide the answer to this one, but at least three of the trials with good results, had high mean levels of initial serum creatinine. Perhaps we need a scoring system to help, prompted by a more detailed examination of all the trial data available.

The bottom line is that it is only worth doing a systematic review and meta-analysis if you are prepared to think.

References:

1 R Birck et al. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. Lancet 2003 362: 598-603.
2 A Zagler et al. N-acetylcysteine and contrast-induced nephropathy: a meta-analysis of 13 randomized trials. American Heart Journal 2006 151: 140-145.

Table 1: Analysis for all trials combined, and sensitivity analyses using different criteria

Types of trial	Number of		CIN rate (%) with		Relative risk (95% CI)	NNTp (95% CI)
	Trials	Patients	NAC	Placebo		
All trials combined	21	3202	11	16	0.7 (0.6 to 0.8)	23 (15 to 51)
In meta-analysis	13	1874	13	18	0.8 (0.6 to 0.9)	22 (13 to 82)
Since meta-analysis	8	1328	9	13	0.6 (0.5 to 0.8)	26 (14 to 220)
Oral only	16	2193	9	13	0.7 (0.6 to 0.9)	26 (15 to 77)
IV ± oral	5	1009	16	22	0.7 (0.6 to 0.9)	16 (9 to 66)
CER ≤12%	10	1409	8	7	1.1 (0.7 to 1.5)	not calculated
CER 12-24%	7	1184	16	19	0.9 (0.7 to 1.1)	not calculated
CER ≥25%	4	609	10	31	0.3 (0.2 to 0.4)	4.7 (3.6 to 6.8)

CER is the control event rate, in this case the CIN incidence with placebo

How good are trials and interventions in knee arthritis?

The reason we do systematic reviews is not only to evaluate how good an intervention may be, but also to examine the clinical utility of the trials we do. The bottom line we have to recognise is that almost all drug trials are performed for some registration purpose, and that the requirements of drug registration are far removed from what is needed in clinical practice.

Those of a more practical bent have therefore either to throw up their hands and walk away from the evidence that exists or to look at that evidence with a cold and fishy eye and criticise constructively. A meta-analysis of interventions for knee osteoarthritis provides an excellent example [1].

Systematic review

The review had a wide search strategy that identified randomised, blinded, placebo-controlled trials of interventions in knee arthritis. The inclusion criteria included use of established diagnostic criteria, including symptom duration of more than three months, and an outcome measure of pain intensity both initially and within four weeks scored on WOMAC pain subscale or 100 mm VAS for global or walking pain.

The main analysis was for the difference between active and placebo during weeks 1-4, using the point with the maximum effect.

Results

The authors found 65 trials with information on 14,060 patients (Table 1). Though trials differed in number and number of patients for each intervention, they were generally similar in terms of the initial pain intensity and mean measurement time for maximum effect, though this was somewhat longer for glucosamine and chondroitin. All trials except two for intra-articular glucocorticoid were of adequate quality to avoid most sources of bias (scoring 3 or more on a five point scale for quality).

What the results show is that some interventions (intra-articular glucocorticoids, topical NSAIDs, opioids, and oral NSAIDs) provide pain relief equivalent to 10-15 mm on a 100 mm VAS scale (Table 1), while others (glucosamine, chondroitin, paracetamol) provide under 5 mm.

Comment

What conclusion can we draw from this? One, which the authors draw, is that perhaps a 10 mm difference over placebo just isn't good enough, and they give some reasons for why we might think that. In essence, then, the conclusion is that the interventions are relatively ineffective.

An alternative view, provided by an accompanying editorial [2], is that common experience is that most of these interventions are known to work well for individual patients in clinical practice. Perhaps, then, the problem is that the trials are unable to capture that benefit, especially in terms of averages – when few patients are average. Here the advice is to question how we do trials or analyse them, and to perhaps consider blaming trial design rather than intervention efficacy.

This is exactly what we want from systematic review: argument, challenge, and new thinking. This is a particularly good example, because it will challenge guidelines, especially in the UK, which rate paracetamol as the first intervention to use, and relegates topical NSAIDs back to the shelf. The evidence makes it hard to justify that view: more thinking needed.

References:

1 JM Bjordal et al. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: a meta-analysis of randomised placebo-controlled trials. European Journal of Pain 2007 11: 125-138.

2 H McQuay, A Moore. Utility of clinical trial results for clinical practice. European Journal of Pain 2007 11: 123-124.

Table 1: Results for short-term interventions for knee osteoarthritis. Best mean difference was the greatest difference between intervention and placebo in the period 1-4 weeks

Intervention	Number of Trials	Number of Patients	Mean initial pain (mm VAS)	Mean time of measurement (weeks)	Best mean difference from placebo (mm VAS)
Intra-articular glucocorticoid (methylprednisolone 40 mg or equivalent)	6	221	57	1.5	15
Topical NSAID	9	749	55	1.6	12
Opioids (30 mg morphine sulphate or equivalent)	6	1057	73	2.8	11
Oral NSAIDs (diclofenac 100 mg or equivalent)	27	9964	64	2.3	10
Glucosamine sulphate (1500 mg)	7	401	58	4.0	5
Chondroitin sulphate (800 mg)	6	362	51	3.6	4
Paracetamol (4000 mg)	4	1306	55	1.3	3

Almotriptan for acute migraine

Migraine is one of those conditions where continuous improvements have been made to outcomes, in this case largely at the prompting of the International Headache Society. Originally the outcome of interest was migraines with initial moderate or severe pain becoming mild pain or no pain by two hours (headache response at two hours).

Later, pain free at two hours was used. Then the goalposts moved to incorporate not just these two hour outcomes, but the additional requirement that patients with the two hour outcome should maintain at least that level of pain relief for 24 hours without additional analgesic medication.

This represents moving goalposts. The hurdle for effectiveness is increasingly higher. One consequence or measure of the increasing difficulty is that response rates with placebo fall from about 40% with the original outcome of two-hour headache response to about 5% for pain free at two hours maintained to 24 hours. An individual patient analysis of almotriptan [1] takes things one step further.

Meta-analysis

The analysis was of four randomised, double-blind, placebo-controlled trials of almotriptan for acute migraine. Several different doses were used, and all analyses estimated efficacy for the first migraine attack.

Results

The four trials had 2,294 patients, of whom 86% were women, and the mean age was 41 years. The main results calculated from data in the paper [1] are shown in Table 1. As expected from other migraine trial data, NNTs were lower (better) with both higher dose of almotriptan, and more easily attained outcome.

One new outcome was the proportion of patients who were pain free at two hours, who were without recurrence of moderate or severe headache pain, who had no additional analgesics before 24 hours, and who reported no adverse events. For this outcome, almotriptan 12.5 mg was successful for 22% of patients, compared with 11% with placebo.

Comment

What we can say is that almotriptan 12.5 mg is about as effective for treating acute migraine as sumatriptan 100 mg, based on short-term outcomes at two hours. As the hurdle gets higher, placebo responses fall (Table 1), just what we have seen before.

What is new is that, using individual patient data, we can now have at least one outcome that has real relevance for patients. We know that 1 in 5 patients who have an acute migraine attack and take the medicine will be pain free at two hours, remain pain free up to 24 hours with no additional analgesic use, and will not have any adverse events.

Pharmaceutical companies may not like the message, because this way of looking at outcomes implies that their drugs are not as good as they would like to think. So be it. But there is another message for people who run or impose formularies: highly limited formularies will mean that only a minority of patients may get the benefits they want, for which of us can say whether those who do not benefit with almotriptan would not benefit with another headache therapy, including other triptans?

References:

1 GC Dahlöf et al. Efficacy, speed of action and tolerability of almotriptan in the acute treatment of migraine: pooled individual patient data from four randomized, double-blind, placebo-controlled clinical trials. Cephalalgia 2006 26: 400-408.

Table 1: Pooled analysis of four randomised trials of almotriptan compared with placebo in a migraine episode with moderate or severe pain

Outcome	Almotriptan dose (mg)	Percent with outcome: Almotriptan	Percent with outcome: Placebo	NNT (95% CI)
Headache response 2 hours	6.25	55	35	5.0 (3.7 to 7.5)
	12.5	61	35	3.8 (3.1 to 5.1)
	25	64	35	3.5 (2.8 to 4.7)
Sustained response 24 hours	6.25	41	27	7.0 (4.8 to 13)
	12.5	45	27	5.5 (4.1 to 8.2)
	25	51	27	4.0 (3.2 to 5.6)
Pain free 2 hours	6.25	29	14	7.0 (5.1 to 11)
	12.5	35	14	4.8 (3.8 to 6.3)
	25	40	14	3.9 (3.1 to 5.1)
Sustained pain free 24 hours	12.5	26	11	6.8 (5.2 to 9.9)
Sustained pain free without adverse events	**12.5**	**22**	**10**	**8.5 (6.2 to 14)**

Mobile phones and cancer

Many of us use mobile telephones to a greater or lesser extent. Because mobile phones emit radio frequencies that can penetrate several centimetres into the human brain, it has been hypothesised that their use could possibly lead to tumours of the head and neck.

This possibility has led to a number of 'scare' stories in the popular press. Typically, debunking the scare involves trying to prove a negative, never an easy thing at the best of times. About the only way to prove a negative is to have very large amounts of data, but also demonstrating the lack of any sort of dose-response as well as no biological plausibility. A large Danish study goes most of the way to doing that for mobile phones and cancer [1].

Study

In the period 1982 to 1995 over 700,000 Danish citizens subscribed to a mobile telephone service. After eliminating those in which individual users could not be identified because they were corporate subscriptions, had incorrect addresses, were from Greenland or the Faroe islands, had a history of previous cancer, or were under 18 years, the final cohort consisted of 420,000 identified subscribers.

Because Denmark has a system of personal identification numbers, cohort members could be linked to files of a cancer registry that is virtually complete, and using a nationwide system of cancer classification. Follow up began from the first day of subscription, and ended on date of diagnosis of any cancer, death, emigration, or end 2002.

Numbers of cancers found were compared with the number expected in the general Danish population, for men and women, and in five-year age groups. Mobile phone subscribers were omitted from this comparison group.

Results

Most (85%) of the 420,000 subscribers were men. The median time of mobile telephone subscription was 8.0 years. Mobile subscribers had 14,250 cases of diagnosed cancer, against an expected number of 15,000, giving an overall standardised incidence ratio of 0.95 (95% confidence interval of 0.93 to 0.97).

For men and women analysed separately there was no difference from expected in all brain and nervous system cancers, or cancers of the salivary glands or eye. For men and women analysed together, there was no increased risk of any type of intracranial cancer, with a hint of a decreased risk for parietal lobe tumours. There was no increase in brain and nervous system tumours and leukaemias according to time from first subscription (Table 1).

There was no increased risk of any other type of cancer for men, with hints of decreased risk for lung, bladder, buccal, oesophageal and liver cancers, as well as other cancers and unspecified cancers. For women the numbers of individual cancers were small, and none had any large increase or decrease in incidence over expected.

Comment

What is good about this study is that it was large, of long duration, covered a whole population, and was performed in Denmark. Denmark has an almost unique ability to successfully link different databases through the use of personal identification numbers.

The results all but eliminates the concept that the use of mobile phones can cause cancer. And not just cancer, because the study allows detailed diagnosis of particular cancer types, including acoustic neuromas and cancers of temporal and parietal lobes which would be the parts of the brain closest to a mobile phone antenna, and hence most at risk.

The paper has a wonderful discussion, which not only puts these results into the context of others, but tells us that the authors could find no studies indicating any biological plausibility for a link between mobile phones and cancer. This comes a close to proving a negative as we are ever likely to get, but even more data will come out in future from continuation and extension of the study.

If you Google mobile phones and cancer, you will find links to over nine million sites. Some are good, some are up to date, but many are not. They should all reflect on the data from Denmark.

Reference:

1 J Schüz et al. Cellular telephone use and cancer risk: update of a nationwide Danish cohort. Journal of the National Cancer Institute 2006 98: 1707-1713.

Table 1: Brain and nervous system cancers, and leukaemias, by years of mobile phone subscription, compared with non-subscribers in Denmark

Years of subscription	Person years	Standardised incidence rate (95%CI)	
		Brain and nervous system	Leukaemia
<1	420,000	0.9 (0.7 to 1.2)	1.1 (0.8 to 1.5)
1-4	1,656,000	1.0 (0.9 to 1.2)	1.1 (0.9 to 1.2)
5-9	1,327,000	1.0 (0.8 to 1.1)	0.9 (0.8 to 1.1)
≥10	170,000	0.7 (0.4 to 0.95)	1.1 (0.7 to 1.5)

Eggs and eyes

Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world. In the USA 200,000 new cases are diagnosed each year, and nearly six million Americans have suffered some vision loss from AMD. A rapidly aging and longer living population suggests that the prevalence of AMD is likely to triple over the next 25 years as our populations contain increasing numbers of older people.

Age is the biggest risk factor, but diets low in antioxidants low in substances like lutein and zeaxanthin may also contribute to both low serum and retinal levels of these antioxidants (Bandolier 123). Higher serum levels are associated with lower incidence of AMD, as are diets high in antioxidants. Spinach and other green and yellow vegetables, as well as egg yolk, have high contents of lutein and zeaxanthin. Recently there has been something of an interest in eggs, so Bandolier has done a quick review.

Egg evidence

Table 1 contains information from six comparative studies of egg supplementation to diets. Most of these were randomised, and most examined dietary supplementation with one egg per day, measuring serum or plasma concentrations of lutein and zeaxanthin, as well as plasma cholesterol subfractions.

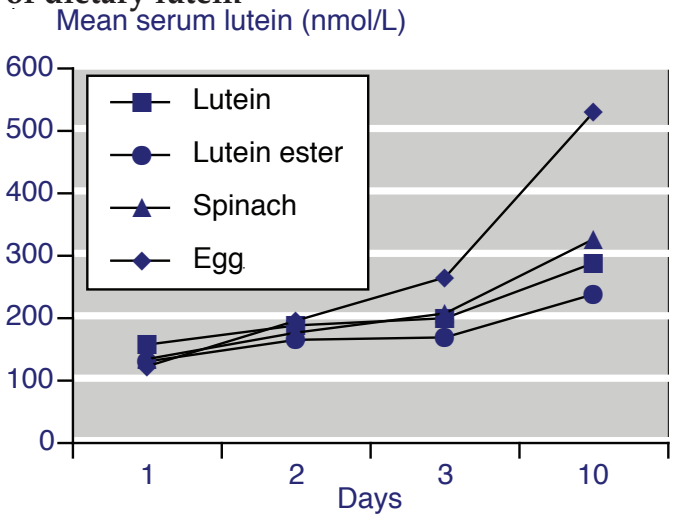
Most studies showed that eating about one egg a day increased serum or plasma lutein by about 20-30%. Only one [1] failed to show any increase in plasma lutein with a standard egg, though it showed a large increase with a "designer" egg from chickens fed a supplemented diet, with 15 times more lutein per egg (1.9 mg) than a standard egg.

Two other results are interesting. One of them [2] compared four diets containing the same amount (6 mg) of daily lutein as a lutein supplement, lutein ester supplement, in spinach, or egg. While the study was small, involving only 10 healthy men in the crossover study, it showed a much higher in-

Table 1: Summary of six trials examining dietary egg and changes to serum lutein and/or zeaxanthin concentrations

Reference	Study	Results
Handelman et al. American Journal of Clinical Nutrition 1999 70: 247-251	Uncontrolled study of 11 subjects aged 48-78 years, mean LDL cholesterol 4.3 mmol/L Two diets for 4.5 weeks separated by 2 weeks, with or without supplementation with 1.3 egg yolks daily	Significant increases in plasma lutein and zeaxanthin: plasma lutein by 28% and 50%, and zeaxanthin by 142% and 114%
Surai et al. European Journal of Clinical Nutrition 2000 54: 298-305.	Randomised, double blind, placebo controlled study in 44 healthy adults aged 26 to 59 years, mean total cholesterol 5.4 mmol/L, HDL cholesterol 1.2 mmol/L Diets were either commercial eggs or "designer" eggs from chickens fed supplemented diet rich in lutein (15x greater lutein content); one egg per day for 8 weeks	No increase in plasma lutein with standard egg, but 100% increase with supplemented egg No significant change in total cholesterol or HDL cholesterol
Chung et al. Journal of Nutrition 2004 134: 1887-1893.	Randomised, open, comparison of four lutein diets in 10 healthy men aged 26 to 75 years, all with total cholesterol below 6.2 mmol/L Four diets tested, lutein and lutein ester supplement, spinach, and egg yolk, each with 6 mg lutein daily for 10 days	Serum lutein increased with all diets: lutein 82% lutein ester 83% spinach 141% egg 323%
Goodrow et al. Journal of Nutrition 2006 136: 2519-2542.	Randomised, open, comparison of two diets in 33 older individuals, mean age 78 years, mean LDL cholesterol 3.1 mmol/L, total cholesterol 5.1 mmol/L Diet periods consisted of no eggs and 1 egg daily for 5 weeks	Serum lutein and zeaxanthin increased by 26% and 38% on 1 egg per day compared with no egg No change in cholesterol in total or subfractions
Wenzel et al. Journal of Nutrition 2006 136: 2568-2573.	Open comparison of placebo pill with diets of standard and high lutein eggs for 12 weeks in 24 women aged 24 to 59 years (randomisation not stated). Initial mean LDL cholesterol 2.6 mmol/L, total cholesterol 4.7 mmol/L	Change in lutein: placebo -10% ordinary egg +23% high lutein egg +26% Change in zeaxanthin: placebo -15% ordinary egg +30% high lutein egg +60% Significant increase in macular pigment optical density with both egg groups No change in serum cholesterol subfractions
Herron et al. Journal of Nutrition 2006 136: 1161-1165.	Randomised comparison of 91 people, mean age 31 years, mean total cholesterol 4.3 mmol/L. Analysis according to genetic subtypes Comparison of 3 eggs daily versus placebo, for 30 days	In 40 patients in whom they were measured, serum lutein increased by about 30% and zeaxanthin by 20%

Figure 1: Change in serum lutein concentrations in 10 healthy men with different sources of dietary lutein



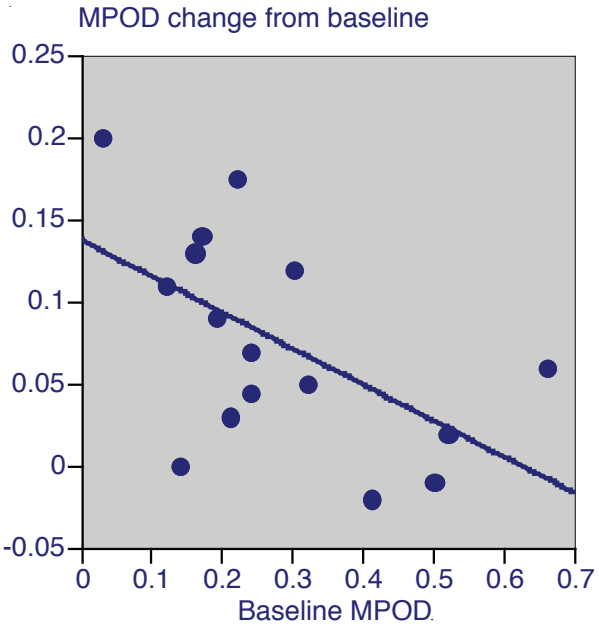
crease in serum lutein for eggs compared with spinach or supplements for the same daily lutein dose (Figure 1).

Only one study has examined the effects of dietary eggs on the retina [3]. Individuals with low macular pigment optical density may be at greater risk of retinal disease because more potentially harmful short wavelength light reaches tissue at the back of the retina. Higher macular pigment optical density is considered, therefore, to be protective. In 24 healthy younger women given placebo or one of two egg diets for 12 weeks, the change in macular pigment optical density was greatest in those with low initial levels (Figure 2).

Comment

Before anyone rushes off to stuff themselves with eggs, it needs to be said that these are early days, though many Internet sites would try and convince readers otherwise. There is no evidence that eggs are a miracle for preventing or curing macular degeneration. What we are seeing is a reasonably consistent response for useful surrogate markers (serum concentrations of lutein and zeaxanthin or macular pigment optical density), without any major change in serum cholesterol or its subfractions.

Figure 2: Change in macular pigment optical density in 24 women over 12 weeks according to baseline value



What is interesting is that lutein in eggs seems to be more readily available, and that any protective effects are likely to be greatest in those with the greatest risk, in this case those with the lowest macular pigment optical density. A good diet, which includes all those leafy greens and some eggs, is still the right advice, for macular degeneration and all sorts of other ills [4].

References:

1 PF Surai et al. Designer egg evaluation in a controlled trial. European Journal of Clinical Nutrition 2000 54: 298-305.

2 HY Chung et al. Lutein bioavailability is higher from lutein-enriched eggs than from supplements and spinach in men. Journal of Nutrition 2004 134: 1887-1893.

3 AJ Wenzel et al. A 12-wk egg intervention increases serum zeaxanthin and macular pigment optical density in women. Journal of Nutrition 2006 136: 2568-2573.

4 JD Ribaya-Mercado, JS Blumberg. Lutein and zeaxanthin and their potential roles in disease prevention. Journal of the American College of Nutrition 2004 23: 567S-587S.

Catheters, infections, and dressings

Infection in hospital, especially in people more seriously ill, is a major problem. Central venous catheters frequently cause bloodstream infection, with up to half a million annually in the USA. Between one in four and one in five bloodstream infections results in death. Epidural catheters also have problems, with deep epidural infection and permanent neurological consequences following epidural abscess. Any intervention that can reduce catheter infections could be of value in helping to minimise serious hospital-acquired infections.

Chlorhexidine gluconate is widely used as a surgical scrub and skin disinfectant, and is now available as a dressing that releases chlorhexidine onto the underlying skin surface over a 10 day period when placed over a catheter exit site. A new meta-analysis indicates that it is likely to be of benefit [1].

Systematic review

Three major electronic databases were searched to the end of 2005 for randomised trials comparing chlorhexidine-impregnated dressings with placebo or povidine-iodine dressings, as well as reference lists. Outcomes were the proportion of patients with exit-site or catheter colonisation with bacteria, and systemic infections like bloodstream or central nervous system infection related to a vascular or epidural catheter.

Results

Eight randomised trials reported on 2,558 patients. Two trials (112 patients) reported on epidurals, and six (2,446) on vascular catheters. None of the trials were blind. All trials used what was essentially a placebo dressing as a comparator, except one trial that used twice-weekly povidine-iodine dressing compared with weekly chlorhexidine dressing. The duration of catheter use varied; usually it was less than a week, but was 17 days on average in one neonatal intensive care study and 67 days on average for patients with tunnelled intravascular catheters for chemotherapy.

The results for bacterial colonisation of exit site or catheter are shown in Figure 1. Overall, the colonisation rate was 27% with control and 14% with chlorhexidine-impregnated dressing. The relative risk was 0.5 (0.45 to 0.62), with a number needed to treat to prevent one colonisation of 8 (6 to 10).

The results for bloodstream or central nervous system infections are shown in Figure 2. Overall, the rate was 3.8% with control and 2.3% with chlorhexidine-impregnated dressing. The relative risk was 0.6 (0.37 to 0.92), with a number needed to treat to prevent one colonisation of 64 (34 to 500). In the four trials which estimated bloodstream infections for vascular catheters only compared with placebo dressing (light symbols in Figure 2), the infection rates were 4.0% and 1.8%, the relative risk 0.4 (0.24 to 0.79), and the number needed to prevent one infection was 44 (26 to 148).

Comment

Clearly this is not a straightforward analysis. It is complicated by considerable clinical heterogeneity, particularly in the types of catheter, patients and circumstances (epidural, vascular; paediatric and adult; surgery, intensive care, cancer treatment). No trial was blind, and not all of them clearly indicated that the results were intention to treat. Moreover, even in total the numbers are limited, with no new trials published since the review to bolster them.

Having said that, the results show a reasonable degree of consistency for a less harmful outcome (exit site or catheter colonisation) and more harmful (bloodstream infection or central nervous system infection) outcome. Catheter-related bloodstream infections are expensive to treat (getting on for £17,000), and have a high mortality. The cost of each chlorhexidine-impregnated dressing is about £2, so even using the upper confidence interval of the NNT to prevent one bloodstream infection (148) indicates a potential for significant cost saving. Spending £300 to save £17,000 and save lives would look good on any health economic analysis, and certainly makes chlorhexidine-impregnated dressing worthy of consideration.

Reference:

1 KM Ho, E Litton. Use of chlorhexidine-impregnated dressing to prevent vascular and epidural catheter colonization and infection: a meta-analysis. Journal of Antimicrobial Chemotherapy 2006 58: 281-287.

Figure 1: Results of individual trials for exit site or catheter colonisation. Dark symbols indicate epidural catheters, half-tone symbol represents povidine control

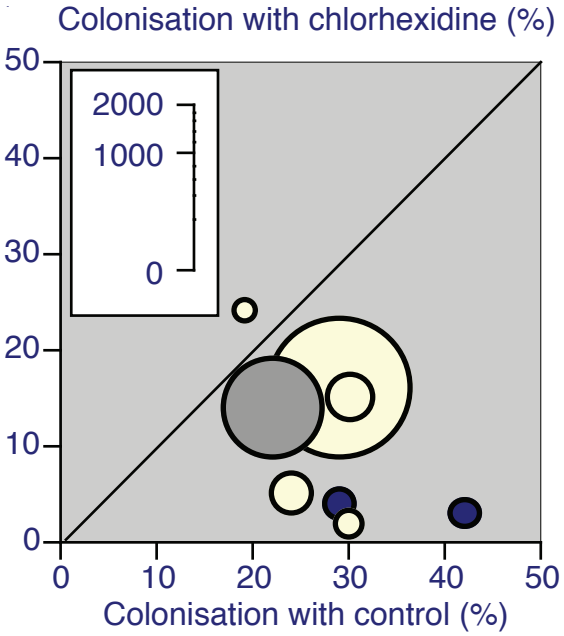
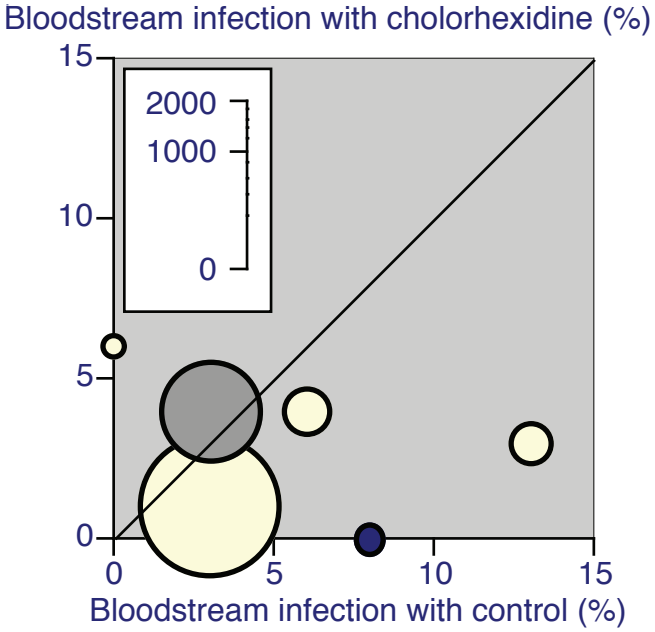


Figure 2: Results of individual trials for bloodstream or central nervous system infections. Dark symbols indicate epidural catheters, half-tone symbol represents povidine control



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